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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,826	WOLFFE ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-36 and 40-73* is/are pending in the application.

4a) Of the above claim(s) *1-7, 10-33 and 44-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7 June 2006 has been entered.

This Office Action is a response to the Paper filed 7 June 2006 in response to the Final Office Action mailed 14 September 2005. Claims 1-7, 10-33 and 44-73 have been withdrawn from consideration and claims 34-36 and 40-43 were considered in the 14 September Office Action. No claim amendments were made in the 7 June Paper. Claims 1-7, 10-36 and 40-73 are pending and claims 34-36 and 40-43 are under consideration.

All objections/rejections not repeated herein are hereby withdrawn.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 42 and 43 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to, "A cell comprising the fusion polypeptide of claim 34 [or the polynucleotide of claim 41]". The specification states, "A host cell is a cell that contains one or more exogenous molecules...Host cells may be ...human cells... and cells *in vivo*." (P. 28, 2nd full ¶.) Thus, the claimed cell, construed as broadly as reasonable in view of the teachings of the specification, reads on a genetically modified cell

present or intended to be present in a human being, said cell becoming integrated into the human being and therefore being an inseparable part of the human itself. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" or limiting the cell to being "isolated" or "cultured" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-36 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. US Pub. No. 2002/0173006 in view of Sassone-Corsi et al. (1999) *Science* 285:886-891 (made of record in the IDS filed 2 July 2002) as evidenced by Chen et al. (1997) *Mol Endocrinol.* 11:3-15, Ebert et al. (1998) *Mol. Cell. Biol.* 18:4089-4096 or Ryuto et al. (1996) *J. Biol. Chem.* 271:28220-28228.

Independent claim 40 is directed to a fusion molecule comprising (a) a DNA-binding domain; and (b) a histone kinase.

Kim et al. teaches chimeric zinc finger proteins with enhanced affinity and specificity that can be used for regulation of gene expression. (See, e.g., ¶0006.) Kim et al. further teaches embodiments of the invention wherein the zinc finger protein is linked to a regulatory domains for regulation of gene expression (¶0109) and explicitly teaches, "Common regulatory domains for addition to the chimeric zinc finger protein made using the methods of the invention include...chromatin associated proteins and their modifiers (e.g., kinases, acetylases and deacetylases)" (¶0110). In paragraph 0116, Kim et al. contemplates histone acetylases and histone deacetylases as specific embodiments of the chimeric zinc finger protein.

Thus, Kim et al. teaches chimeric zinc finger proteins comprising various activation or regulatory domains, contemplates chromatin associated proteins and their modifiers as regulatory domains that can be added, and specifically identifies the histone modifying enzymes (i.e., histone acetyltransferase and histone deacetylase) as transcriptional regulators that can be comprised in the chimeric molecules. Kim et al. further teaches that the chimeric zinc finger

proteins comprising regulatory domains contemplated therein are useful for the modulation of gene expression. (See also the first sentence in ¶0109.)

Kim et al. does not explicitly teach a regulatory domain that is a histone kinase.

Sassone-Corsi et al. teach isolation of Rsk-2 and demonstrate that the protein is an H3 histone kinase. (See especially the paragraph bridging the left and middle columns on page 887, Figure 2 and the caption thereto.) Sassone-Corsi et al. further teaches a nucleic acid construct encoding a human Rsk-2 that can be used in the construction of a chimeric zinc finger protein as taught by Kim et al. (See, e.g., Fig. 5 and the caption thereto.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a chimeric zinc finger DNA binding protein comprising a regulatory domain according to the teachings of Kim et al., wherein the regulatory domain is the H3 histone kinase Rsk-2 as described by Sassone-Corsi et al.

Motivation to combine these teachings is found in the nature of the problem solved by the chimeric zinc finger proteins of Kim et al., which is stated to be for the purpose of modulating gene expression, and from the teachings of Sassone-Corsi et al., which state, "Remodeling of chromatin structure appears to have a primary role in transcriptional regulation [], and posttranslational modifications of histones are thought to contribute to this remodeling...rapid and transient phosphorylation of a subset of histoneH3 molecules correlates with the activated expression of immediate-early genes such as c-*fos* and c-*jun* in mammalian cells after mitogen stimulation []. These observations suggest that H3 phosphorylation may contribute to chromatin remodeling during mitosis and transcriptional activation." (Paragraph bridging pp. 886-887, citations omitted.)

Thus, one would have been motivated use the histone kinase of Sassone-Corsi et al. in order to obtain the expected benefit of chromatin remodeling and regulated gene expression as taught by Sassone-Corsi et al.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Kim et al. teaches various methods of constructing proteins comprising functionally associated zinc finger DNA binding domains and heterologous regulatory domains (see especially ¶0109), which methods were routinely practiced in the art.

For these reasons, the invention of independent claim 40, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims are also found in the cited art. As discussed above, Kim et al. teaches fusion proteins comprising a zinc finger protein DNA binding domain and a regulatory domain, which meets the limitations of claims 34 and 35.

Claim 36 is directed to the polypeptide of claim 34 wherein the DNA binding domain binds to a target site in one of a variety of genes. Kim et al. teaches that the zinc finger proteins described therein can be targeted to specific sites in DNA and explicitly contemplates regulatory sites such as SP-1 and hypoxia response elements as desirable target sites. (See especially ¶0035.) As evidenced by Chen et al. (teaching the androgen receptor gene promoter comprises an SP-1 site), Ryuto et al. (teaching that the VEGF gene contains several SP-1 sites) and Ebert et al. (teaching that the EPO 3' enhancer comprises a HIF-1 site), the SP-1 and hypoxia response element targeted proteins contemplated by Kim et al. would bind to a target sequence in many of the genes recited in claim 36. Therefore, the claim is also obvious over the teachings of Kim et al. and Sassone-Corsi et al.

Finally, claim 41 is directed to a polynucleotide encoding the fusion protein of claim 34 and claims 42-43 are directed to cells comprising the polypeptide of claim 34 and the polynucleotide of claim 41, respectively. The limitations of claims 41-43 are obvious over the cited art because in the section entitled, "IV. Expression and Purification of Zinc Finger Proteins made using the Methods of the Invention", Kim et al. teaches expression of the polypeptides in host cells from recombinant nucleic acid constructs, which constructs and host cells render obvious claims 41-43.

In view of the foregoing, the invention of claims 40-43 and 34-36, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 34-36 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. US Pub. No. 2002/0173006 in view of Rea et al. (10 August 2000) *Nature* 406:593-599 (made of record in the IDS filed 2 July 2002) as evidenced by Chen et al. (1997) *Mol Endocrinol.* 11:3-15, Ebert et al. (1998) *Mol. Cell. Biol.* 18:4089-4096 or Ryuto et al. (1996) *J. Biol. Chem.* 271:28220-28228.

Independent claim 40 is directed to a fusion molecule comprising (a) a DNA-binding domain; and (b) a histone methyltransferase.

Kim et al. teaches chimeric zinc finger proteins with enhanced affinity and specificity that can be used for regulation of gene expression. (See, e.g., ¶0006.) Kim et al. further teaches embodiments of the invention wherein the zinc finger protein is linked to a regulatory domains for regulation of gene expression (¶0109) and explicitly teaches, "Common regulatory domains

for addition to the chimeric zinc finger protein made using the methods of the invention include...chromatin associated proteins and their modifiers (e.g., kinases, acetylases and deacetylases)" (¶0110). In paragraph 0116, Kim et al. contemplates histone acetylases and histone deacetylases as specific embodiments of the chimeric zinc finger protein.

Thus, Kim et al. teaches chimeric zinc finger proteins comprising various activation or regulatory domains, contemplates chromatin associated proteins and their modifiers as regulatory domains that can be added, and specifically identifies the histone modifying enzymes (i.e., histone acetyltransferase and histone deacetylase) as transcriptional regulators that can be comprised in the chimeric molecules. Kim et al. further teaches that the chimeric zinc finger proteins comprising regulatory domains contemplated therein are useful for the modulation of gene expression. (See also the first sentence in ¶0109.)

Kim et al. does not explicitly teach a regulatory domain that is a histone methyltransferase.

Rea et al. demonstrates that the mammalian protein Suv39h1 is an H3 histone methyltransferase. (See throughout, especially p. 595, ¶1.) Rea et al. further teaches that nucleic acids encoding SUV39H1 proteins suitable for recombinant DNA manipulations are available in the art as evidenced by the experiments performed using HeLa cell lines overexpressing epitope tagged SUV39H1. (See especially p. 598, col. 2, 1st full ¶.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a chimeric zinc finger DNA binding protein comprising a regulatory domain according to the teachings of Kim et al., wherein the regulatory domain is the H3 histone methyltransferase SUV39H1 as described by Rea et al.

Motivation to combine these teachings is found in the nature of the problem solved by the chimeric zinc finger proteins of Kim et al., which is stated to be for the purpose of modulating gene expression, and from the teachings of Rea et al., which state, "Higher-order chromatin structure is essential for epigenetic gene control and for the functional organization of chromosomes. Differences in higher-order chromatin structure have been linked with distinct covalent modifications of histone tails that regulate transcriptional 'on' or 'off' states..." (p. 593, ¶1), "Here we report that mammalian SUV39H1 or suv39h proteins are SET-domain-dependent, H3-specific histone methyltransferases (HMTases) which selectively methylate lysine 9 (lys9) of the H3 N terminus—a modification that appears intrinsically linked to the organization of higher-order chromatin" (p. 593, bridging col. 1-2) and "On the basis of our results, we propose that SU(VAR)3-9 related proteins provide important enzymatic activities towards the induction and assembly of higher-order chromatin" (p. 598, col. 2, 1st full sentence).

Thus, one would have been motivated use the histone methyltransferase of Rea et al. in order to obtain the expected benefit of chromatin remodeling and regulation of transcriptional 'on' or 'off' states as taught by Rea et al.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Kim et al. teaches various methods of constructing proteins comprising functionally associated zinc finger DNA binding domains and heterologous regulatory domains (see especially ¶0109), which methods were routinely practiced in the art.

For these reasons, the invention of independent claim 40, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims are also found in the cited art. As discussed above, Kim et al. teaches fusion proteins comprising a zinc finger protein DNA binding domain and a regulatory domain, which meets the limitations of claims 34 and 35.

Claim 36 is directed to the polypeptide of claim 34 wherein the DNA binding domain binds to a target site in one of a variety of genes. Kim et al. teaches that the zinc finger proteins described therein can be targeted to specific sites in DNA and explicitly contemplates regulatory sites such as SP-1 and hypoxia response elements as desirable target sites. (See especially ¶0035.) As evidenced by Chen et al. (teaching the androgen receptor gene promoter comprises an SP-1 site), Ryuto et al. (teaching that the VEGF gene contains several SP-1 sites) and Ebert et al. (teaching that the EPO 3' enhancer comprises a HIF-1 site), the SP-1 and hypoxia response element targeted proteins contemplated by Kim et al. would bind to a target sequence in many of the genes recited in claim 36. Therefore, the claim is also obvious over the teachings of Kim et al. and Rea et al.

Finally, claim 41 is directed to a polynucleotide encoding the fusion protein of claim 34 and claims 42-43 are directed to cells comprising the polypeptide of claim 34 and the polynucleotide of claim 41, respectively. The limitations of claims 41-43 are obvious over the cited art because in the section entitled, "IV. Expression and Purification of Zinc Finger Proteins made using the Methods of the Invention", Kim et al. teaches expression of the polypeptides in host cells from recombinant nucleic acid constructs, which constructs and host cells render obvious claims 41-43.

In view of the foregoing, the invention of claims 40-43 and 34-36, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 34-36 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. US Pub. No. 2002/0173006 in view of Cai *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96:2828-2833 (made of record in the IDS filed 7 June 2006) as evidenced by Chen et al. (1997) *Mol Endocrinol.* 11:3-15, Ebert et al. (1998) *Mol. Cell. Biol.* 18:4089-4096 or Ryuto et al. (1996) *J. Biol. Chem.* 271:28220-28228.

Independent claim 40 is directed to a fusion molecule comprising (a) a DNA-binding domain; and (b) a histone de-ubiquitinating enzyme.

Kim et al. teaches chimeric zinc finger proteins with enhanced affinity and specificity that can be used for regulation of gene expression. (See, e.g., ¶0006.) Kim et al. further teaches embodiments of the invention wherein the zinc finger protein is linked to a regulatory domains for regulation of gene expression (¶0109) and explicitly teaches, "Common regulatory domains for addition to the chimeric zinc finger protein made using the methods of the invention include...chromatin associated proteins and their modifiers (e.g., kinases, acetylases and deacetylases)" (¶0110). In paragraph 0116, Kim et al. contemplates histone acetylases and histone deacetylases as specific embodiments of the chimeric zinc finger protein.

Thus, Kim et al. teaches chimeric zinc finger proteins comprising various activation or regulatory domains, contemplates chromatin associated proteins and their modifiers as regulatory domains that can be added, and specifically identifies the histone modifying enzymes (i.e.,

histone acetyltransferase and histone deacetylase) as transcriptional regulators that can be comprised in the chimeric molecules. Kim et al. further teaches that the chimeric zinc finger proteins comprising regulatory domains contemplated therein are useful for the modulation of gene expression. (See also the first sentence in ¶0109.)

Kim et al. does not explicitly teach a regulatory domain that is a histone de-ubiquitinating enzyme.

Cai et al. teach isolation and cloning of Ubp-M and demonstrate that the protein is a histone H2A de-ubiquitinating enzyme. (See especially the Abstract; p. 2833, ¶2; Fig. 7 and the caption thereto.) Cai et al. further teaches a nucleic acid construct encoding a Ubp-M protein that can be used in the construction of a chimeric zinc finger protein as taught by Kim et al. (See especially p. 2828, col. 2, 4th full ¶; Fig. 1A; and the footnote "Data deposition" on p. 2828.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a chimeric zinc finger DNA binding protein comprising a regulatory domain according to the teachings of Kim et al., wherein the regulatory domain is the histone de-ubiquitinating enzyme Ubp-M as described by Cai et al.

Motivation to combine these teachings is found in the nature of the problem solved by the chimeric zinc finger proteins of Kim et al., which is stated to be for the purpose of modulating gene expression, and from the teachings of Cai et al., which state, "[R]ecent studies suggest that deubiquitinating enzymes are involved in regulating transcriptional activity of chromatin..." (P. 2828, col. 2, ll. 5-7.)

Thus, one would have been motivated use the histone de-ubiquitinating enzyme of Cai et al. in order to obtain the expected benefit of chromatin remodeling and regulated gene expression as taught by Cai et al.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Kim et al. teaches various methods of constructing proteins comprising functionally associated zinc finger DNA binding domains and heterologous regulatory domains (see especially ¶0109), which methods were routinely practiced in the art.

For these reasons, the invention of independent claim 40, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims are also found in the cited art. As discussed above, Kim et al. teaches fusion proteins comprising a zinc finger protein DNA binding domain and a regulatory domain, which meets the limitations of claims 34 and 35.

Claim 36 is directed to the polypeptide of claim 34 wherein the DNA binding domain binds to a target site in one of a variety of genes. Kim et al. teaches that the zinc finger proteins described therein can be targeted to specific sites in DNA and explicitly contemplates regulatory sites such as SP-1 and hypoxia response elements as desirable target sites. (See especially ¶0035.) As evidenced by Chen et al. (teaching the androgen receptor gene promoter comprises an SP-1 site), Ryuto et al. (teaching that the VEGF gene contains several SP-1 sites) and Ebert et al. (teaching that the EPO 3' enhancer comprises a HIF-1 site), the SP-1 and hypoxia response element targeted proteins contemplated by Kim et al. would bind to a target sequence in many of the genes recited in claim 36. Therefore, the claim is also obvious over the teachings of Kim et al. and Cai et al.

Finally, claim 41 is directed to a polynucleotide encoding the fusion protein of claim 34 and claims 42-43 are directed to cells comprising the polypeptide of claim 34 and the polynucleotide of claim 41, respectively. The limitations of claims 41-43 are obvious over the cited art because in the section entitled, "IV. Expression and Purification of Zinc Finger Proteins made using the Methods of the Invention", Kim et al. teaches expression of the polypeptides in host cells from recombinant nucleic acid constructs, which constructs and host cells render obvious claims 41-43.

In view of the foregoing, the invention of claims 40-43 and 34-36, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 34-36 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. US Pub. No. 2002/0173006 in view of Kaiser et al. (1994) *J. Biol. Chem.* 269:8797-8802 (made of record in the IDS filed 7 June 2006) and further in view of Cai *et al.* (*supra*) as evidenced by Chen et al. (1997) *Mol Endocrinol.* 11:3-15, Ebert et al. (1998) *Mol. Cell. Biol.* 18:4089-4096 or Ryuto et al. (1996) *J. Biol. Chem.* 271:28220-28228.

Independent claim 40 is directed to a fusion molecule comprising (a) a DNA-binding domain; and (b) a histone ubiquitinating enzyme.

Kim et al. teaches chimeric zinc finger proteins with enhanced affinity and specificity that can be used for regulation of gene expression. (See, e.g., ¶0006.) Kim et al. further teaches embodiments of the invention wherein the zinc finger protein is linked to a regulatory domains for regulation of gene expression (¶0109) and explicitly teaches, "Common regulatory domains

for addition to the chimeric zinc finger protein made using the methods of the invention include...chromatin associated proteins and their modifiers (e.g., kinases, acetylases and deacetylases)" (¶0110). In paragraph 0116, Kim et al. contemplates histone acetylases and histone deacetylases as specific embodiments of the chimeric zinc finger protein.

Thus, Kim et al. teaches chimeric zinc finger proteins comprising various activation or regulatory domains, contemplates chromatin associated proteins and their modifiers as regulatory domains that can be added, and specifically identifies the histone modifying enzymes (i.e., histone acetyltransferase and histone deacetylase) as transcriptional regulators that can be comprised in the chimeric molecules. Kim et al. further teaches that the chimeric zinc finger proteins comprising regulatory domains contemplated therein are useful for the modulation of gene expression. (See also the first sentence in ¶0109.)

Kim et al. does not explicitly teach a regulatory domain that is a histone ubiquitinating enzyme.

Kaiser et al. teach isolation and cloning of UbcH2 and demonstrate that the protein is a histone ubiquitinating enzyme. (See especially the discussion commencing in the paragraph bridging col. 1-2 on p. 8799 and Fig. 6 and the caption thereto.) Kaiser et al. further teaches a nucleic acid encoding a human UbcH2 that can be used in the construction of a chimeric zinc finger protein as taught by Kim et al. (See, e.g., Fig. 1 and the caption thereto.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a chimeric zinc finger DNA binding protein comprising a regulatory domain according to the teachings of Kim et al., wherein the regulatory domain is the histone ubiquitinating enzyme as described by Kaiser et al.

Motivation to combine these teachings is found in the nature of the problem solved by the chimeric zinc finger proteins of Kim et al., which is stated to be for the purpose of modulating gene expression, and from the knowledge available to one of skill in the art at the time the instant invention was made. Specifically, as discussed above, the teachings of Cai *et al.* suggest that the ubiquitination state of histones is involved in regulating transcriptional activity of chromatin.

Thus, one would have been motivated use the histone ubiquitinating enzyme of Kaiser et al. in order to obtain the expected benefit of chromatin remodeling and regulated gene expression as taught by Cai et al.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Kim et al. teaches various methods of constructing proteins comprising functionally associated zinc finger DNA binding domains and heterologous regulatory domains (see especially ¶0109), which methods were routinely practiced in the art.

For these reasons, the invention of independent claim 40, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims are also found in the cited art. As discussed above, Kim et al. teaches fusion proteins comprising a zinc finger protein DNA binding domain and a regulatory domain, which meets the limitations of claims 34 and 35.

Claim 36 is directed to the polypeptide of claim 34 wherein the DNA binding domain binds to a target site in one of a variety of genes. Kim et al. teaches that the zinc finger proteins described therein can be targeted to specific sites in DNA and explicitly contemplates regulatory sites such as SP-1 and hypoxia response elements as desirable target sites. (See especially ¶0035.) As evidenced by Chen et al. (teaching the androgen receptor gene promoter comprises an

SP-1 site), Ryuto et al. (teaching that the VEGF gene contains several SP-1 sites) and Ebert et al. (teaching that the EPO 3' enhancer comprises a HIF-1 site), the SP-1 and hypoxia response element targeted proteins contemplated by Kim et al. would bind to a target sequence in many of the genes recited in claim 36. Therefore, the claim is also obvious over the teachings of Kim et al. and Kaiser et al.

Finally, claim 41 is directed to a polynucleotide encoding the fusion protein of claim 34 and claims 42-43 are directed to cells comprising the polypeptide of claim 34 and the polynucleotide of claim 41, respectively. The limitations of claims 41-43 are obvious over the cited art because in the section entitled, "IV. Expression and Purification of Zinc Finger Proteins made using the Methods of the Invention", Kim et al. teaches expression of the polypeptides in host cells from recombinant nucleic acid constructs, which constructs and host cells render obvious claims 41-43.

In view of the foregoing, the invention of claims 40-43 and 34-36, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 34-36 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. US Pub. No. 2002/0173006 in view of Zhao *et al.* (1994) *Biochem. Mol. Biol. Int.* 34:1027-1033 (made of record in the IDS filed 7 June 2006) and further in view of Spencer et al. (1999) *Gene* 240:1-12 as evidenced by Chen et al. (1997) *Mol Endocrinol.* 11:3-15, Ebert et al. (1998) *Mol. Cell. Biol.* 18:4089-4096 or Ryuto et al. (1996) *J. Biol. Chem.* 271:28220-28228.

Independent claim 40 is directed to a fusion molecule comprising (a) a DNA-binding domain; and (b) a histone phosphatase.

Kim et al. teaches chimeric zinc finger proteins with enhanced affinity and specificity that can be used for regulation of gene expression. (See, e.g., ¶0006.) Kim et al. further teaches embodiments of the invention wherein the zinc finger protein is linked to a regulatory domains for regulation of gene expression (¶0109) and explicitly teaches, "Common regulatory domains for addition to the chimeric zinc finger protein made using the methods of the invention include...chromatin associated proteins and their modifiers (e.g., kinases, acetylases and deacetylases)" (¶0110). In paragraph 0116, Kim et al. contemplates histone acetylases and histone deacetylases as specific embodiments of the chimeric zinc finger protein.

Thus, Kim et al. teaches chimeric zinc finger proteins comprising various activation or regulatory domains, contemplates chromatin associated proteins and their modifiers as regulatory domains that can be added, and specifically identifies the histone modifying enzymes (i.e., histone acetyltransferase and histone deacetylase) as transcriptional regulators that can be comprised in the chimeric molecules. Kim et al. further teaches that the chimeric zinc finger proteins comprising regulatory domains contemplated therein are useful for the modulation of gene expression. (See also the first sentence in ¶0109.)

Kim et al. does not explicitly teach a regulatory domain that is a histone phosphatase.

Zhao et al. teaches a recombinant protein phosphatase-1 having histone phosphatase activity. (See especially the Abstract, Table I and Figures 1-2.) Zhao et al. the availability of a recombinant protein phosphatase-1 that can be used in the construction of a chimeric zinc finger protein as taught by Kim et al. (See especially p. 1028, ¶1.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a chimeric zinc finger DNA binding protein comprising a regulatory domain according to the teachings of Kim et al., wherein the regulatory domain is the protein phosphatase-1 as described by Zhao et al.

Motivation to combine these teachings is found in the nature of the problem solved by the chimeric zinc finger proteins of Kim et al., which is stated to be for the purpose of modulating gene expression, and from the knowledge available in the art at the time the instant invention was made. Specifically, Spencer *et al.* teaches, "Several studies show an involvement of H1 phosphorylation in gene transcription" (p. 8, ¶ bridging col. 1-2) and, "Protein phosphatase 1 appears to be the H1 and H3 phosophatase []" (p. 9, ll. 19-20).

Thus, one would have been motivated use the histone phosphatase of Zhao et al. in order to obtain the expected benefit of chromatin remodeling and regulated gene expression as taught by Spencer et al.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Kim et al. teaches various methods of constructing proteins comprising functionally associated zinc finger DNA binding domains and heterologous regulatory domains (see especially ¶0109), which methods were routinely practiced in the art.

For these reasons, the invention of independent claim 40, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of the dependent claims are also found in the cited art. As discussed above, Kim et al. teaches fusion proteins comprising a zinc finger protein DNA binding domain and a regulatory domain, which meets the limitations of claims 34 and 35.

Claim 36 is directed to the polypeptide of claim 34 wherein the DNA binding domain binds to a target site in one of a variety of genes. Kim et al. teaches that the zinc finger proteins described therein can be targeted to specific sites in DNA and explicitly contemplates regulatory sites such as SP-1 and hypoxia response elements as desirable target sites. (See especially ¶0035.) As evidenced by Chen et al. (teaching the androgen receptor gene promoter comprises an SP-1 site), Ryuto et al. (teaching that the VEGF gene contains several SP-1 sites) and Ebert et al. (teaching that the EPO 3' enhancer comprises a HIF-1 site), the SP-1 and hypoxia response element targeted proteins contemplated by Kim et al. would bind to a target sequence in many of the genes recited in claim 36. Therefore, the claim is also obvious over the teachings of Kim et al. and Zhao et al.

Finally, claim 41 is directed to a polynucleotide encoding the fusion protein of claim 34 and claims 42-43 are directed to cells comprising the polypeptide of claim 34 and the polynucleotide of claim 41, respectively. The limitations of claims 41-43 are obvious over the cited art because in the section entitled, "IV. Expression and Purification of Zinc Finger Proteins made using the Methods of the Invention", Kim et al. teaches expression of the polypeptides in host cells from recombinant nucleic acid constructs, which constructs and host cells render obvious claims 41-43.

In view of the foregoing, the invention of claims 40-43 and 34-36, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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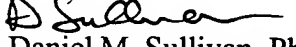

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